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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,350	01/27/2006	Tetsuro Tateishi	KUZ0028USNP	2515

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LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
PURDY, KYLE A	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
02/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

Office Action Summary	Application No.	Applicant(s)	
	10/566,350	TATEISHI ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2008*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-9, 11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The Examiner acknowledges receipt of the amendments filed on 12/22/2008 wherein claim 1 has been amended and claims 2 has been cancelled.

2. Claims 1, 3-9, 11 and 13-20 are presented for examination on the merits. The following rejections are made.

3. Applicant has pointed out that Form-326 mailed to Applicant on 10/16/2008 indicated claim 12 as pending. The Examiner erred. Claim 12 should not have been listed as pending as it was already cancelled.

Response to Applicants' Arguments

4. Applicants arguments filed 12/22/2008 regarding the rejection of claim 2 made by the Examiner under 35 USC 103(a) over Modiamo et al. (int. J. Pharmaceutics, 1998) in view of Hirano et al. (US 6495159) and Higo et al. (US 5866157), evidenced by Walters (Transdermal Drug delivery, 1989) have been fully considered and they are found persuasive. This rejection has been overcome by cancellation of the claim.

5. Applicants arguments filed 12/22/2008 regarding the rejection of claims 1, 3-9, 11 and 13-20 made by the Examiner under 35 USC 103(a) over Modiamo et al. (int. J. Pharmaceutics, 1998) in view of Hirano et al. (US 6495159) and Higo et al. (US 5866157), evidenced by Walters (Transdermal Drug delivery, 1989) have been fully considered but they are not found persuasive.

6. The rejection of claims 1, 3-9, 11 and 13-20 made by the examiner under 35 USC 103(a) is MAINTAINED for the reasons of record in the office action mailed on 10/16/2008.

7. In regards to the 103(a) rejection, Applicant asserts the following:

A) Application of Hirano is improper because it does not teach the drug as being present in the adhesive layer of the patch and thus would provide no motivation to formulate an adhesive layer comprising the drug.

B) Higo teaches an adhesive layer distinct from the adhesive layer of the present claims. Higo does not teach an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid compositing a carboxyl group in the adhesive layer.

C) Comparative Example 2 of the instant application demonstrates that an adhesive patch comprising 2-ethylhexylacrylate/vinyl acetate copolymer shows inferior adhesive properties as compared to a patch with an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group and that 2-ethylhexyl acrylate/vinyl acetate/hydroxyethyl acrylate shows low drug stability compared to the acrylic polymers of the invention.

8. With respect to A, it's duly noted that Hirano teaches the drug being contained in a storage compartment between the backing and adhesive layers. However, it's pointed out that the adhesive layer is described as the 'drug release layer' wherein said drug release layer constitutes a pressure-sensitive adhesive layer capable of controlling the release of drug. Thus, while it may be true that the patch formulation of Hirano has a storage layer, the adhesive layer, as it is the drug releasing layer, would necessarily have drug present in it. How else would the pharmaceutical actives be delivered to the subject in need? The instant claim is open in that it uses 'comprising' language. Such language would not exclude a patch formulation with drug in other areas of the patch, that is, the instant claim does not limit drug to only be present in the

adhesive layer. In the case that Applicant does not find this argument persuasive, Applicant is directed to the other secondary teaching to Higo which is directed to matrix patch formulations for the release of drugs into the skin. The patch formulations possess an adhesive layer that contains the active agent. Thus, even if Hirano would not suggest or motivate a person of ordinary skill in the art to have drug in the adhesive layer, a person would be motivated to include drug in the adhesive layer, as it was already known in the art at the time the present invention was made, to be suitable for storage of the drug. Applicants argument is not found persuasive.

9. With respect to B, the Examiner agrees that Higo does not teach the instantly claimed acrylic adhesives. However, Higo is not relied upon to cure the deficiency in regard to the acrylic adhesive polymers, Hirano is. Rather, Higo is relied upon for its teaching of matrix patch formulations, patch structure and inclusion of transdermal penetration enhancers. Applicants argument is not found persuasive.

10. With respect to C, the Examples which Applicant cites have no impact on the present obviousness rejection. The fact that one copolymer has inferior adhesive properties does not mitigate the instant rejection. And the showing that one copolymer possess low drug stability does not illustrate unexpected results for an entire class of copolymers. The class of copolymers as required by the instant application, i.e. an acrylic polymer obtained by copolymerization of a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group is obvious over Hirano. Hirano teaches such copolymerization products as useful adhesive agents for patch formulations and contemplates the instantly claimed acrylic monomers, e.g. 2-ethylhexyl acrylate, vinyl acetate, acrylic acid and butyl acrylate. Reading a list and selecting from

disclosed compounds, in this case acrylic monomers, is no more ingenious than selecting the last piece to put in the last opening of a jigsaw puzzle. See MPEP 2144.07. Applicants arguments are not found persuasive.

Maintained Rejections, of Record
Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 3-9, 11, 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modamio et al. (International Journal of Pharmaceutics, 1998, 173, 141-148; of record) in view of Hirano et al. (US 6495159; of record) and Higo et al. (US 5866157; of record), further evidenced by Walters (Transdermal Drug Delivery, 1989, New York, NY, pp. 197-246; of record).

13. Modiamo is a study pertaining to the penetration rate of bisoprolol fumarate across a section of human skin. It is taught that bisoprolol is a beta-blocker, and that research is underway to develop transdermal patches for the efficient delivery of beta-blockers such as bisoprolol (and celiprolol) for patients who cannot take medicines by themselves or when oral administration of such drugs may be inadvisable due to unpleasant side effects (see page 142, column 1, 1st paragraph; see instant claim 1). It is taught that the drug is applied to a surface area of 16 cm^2 (see page 144, column 2, 3rd paragraph) wherein the drug possesses a penetration rate of

1.19±060 μg/hr/cm^2 (see abstract). It is noted that the penetration rate approaches 3.0 μg/hr/cm^2 when taking into account three standard deviations (see instant claims 1 and 16). Modamios experiments indicate that bisoprolol has a difficult time crossing the skin barrier, and the theoretical plasma concentration provided by the system is well below bisoprolols therapeutic concentration (see abstract). It is stated that in order to for the bisoprolol containing patch to be therapeutically effective, transdermal absorption enhancers are required to improve bisoprolols diffusion across human skin (see abstract and page 147, first column, third paragraph; see instant claim 7). Modamio incorporates by reference the teaching of Walters to illustrate typical absorption enhancers which include solvents like water and lower alcohols, surfactants such as fatty acids and fatty alcohols, and other chemicals such as urea (see pages 203-227).

14. Modamo fails to teach the patch that possesses an matrix type adhesive layer, wherein the adhesive layer contains an acrylic polymer obtained by copolymerizing a meth(acrylic ester with a (meth)acrylic acid comprising a carboxyl group such as that of 2-ethylhexyl acrylate-butyl acrylate-acrylic acid copolymer. The teaching of Modamio fails to teach the rate of penetration of bisoprolol through the skin as 4.0-300 μg/hr/cm^2. Modamio also fails to specifically teach the absorption promoters as being for example, lauryl alcohol, an organic acid or isopropyl myristate.

15. Hirano is drawn to a percutaneous treatment device that possesses a pressure-sensitive adhesive acrylic polymer layer that allows for the controlled release of a medicine (see column 1, lines 9-10). The acrylic adhesive taught by Hirano may be a copolymer of (meth)acrylic acid alkyl ester monomers and other functional monomers (see column 6, lines 25-31). The (meth)acrylic acid alkyl ester monomers include butyl acrylate, 2-ethylhexyl acrylate, and 2-

ethylhexyl methacrylate (see instant claims 1-3, 13, 15, 17, and 19). The functional monomer is said to be a monomer having a carboxylic acid such as acrylic acid, methacrylic acid (see column 6, lines 47-51; see instant claims 1-3). Furthermore, it is taught in Example 1 and 2 that vinyl acetate may be implemented as a monomer in the copolymer (see instant claim 18). For example, it is present in the copolymer of 2-ethylhexyl acrylate/ethylacrylate/vinyl acetate copolymer (see Example 2). Moreover, the idea of combining an acrylic copolymer with an elastomeric polymer is expressly taught at column 5, lines 43 to line 6 column 3. Specifically, Hirano discloses the use of polyisobutylene (available from Exxon chemical as trade name "Vistanex") and styrene-isoprene-styrene copolymer (available from Japan Synthetic Rubber Co. as "JSR 5000") (see instant claim 6). The reference also teaches the use of aliphatic acids, aliphatic alcohols and esters of aliphatic acids having 7-20 carbon atoms (see column 4, lines 42-56; see instant claims 7-9). Some specific examples of disclosed absorption promoters include lauryl and myristyl alcohol. Further, Hirano teaches a patch (see abstract and Figure 1) that possess a backing layer (i.e. drug permeable membrane) which is in direct contact with the adhesive layer (see instant claim 20).

16. Higo is drawn to a matrix patch formulation which comprises an adhesive layer containing a physiological active substance, an organic acid, a hydrophobic material, a tackifying resin, a plasticizer and an absorption enhancer (see abstract). The absorption enhancers (and organic acids) are included in the formulations taught by Higo in order to allow for sufficient uptake of physiological active material from the skin by improving the transdermal mobility for said active substances (see column 1, lines 35-40). Absorption enhancers taught by Higo include

organic acids such as lactic acid (see column 2, lines 62-66 and column 3, lines 12-19) as well as the absorption enhancer isopropyl myristate (see column 5, line 11; see instant claims 7-9).

17. Thus, it would have been obvious to one of ordinary skill, at the time the invention was made to combine the references of Modamio with Hirano and Higo because in doing so would result in a transdermal matrix type patch that possesses improved adhesive properties while allowing for the modulated release (and improved absorption properties) of the active substance, bisoprolol. The significance of Modamio is that the reference suggests using a transdermal patch for the delivery of bisoprolol wherein bisoprolol has a penetration rate of 1.19±060 μg/hr/cm^2 across the skin. Albeit true that Modiamo fails to teach a transdermal patch explicitely, Modiamo does states that the transdermal pathway is of interest for the administration of the drugs being studied. Such a recitation would motivate an ordinarily skilled artesian to look to the art so as to identify a structure capable of supporting such a transdermal delivery system. With respect to the penetration rate of bisoprolol, it is also noted that this value is below the instantly claimed rates. However, Modiamo teaches that this rate could be increased by adding absorption enhancers. Additionally, Higo and Hirano also teach using penetration enhancers in their compositions to aid in the penetration rate. The notion of implementing an acrylic adhesive layer for the delivery of bisoprolol is obvious because one would want the patch to be capable of effectively adhering to the skin for constant delivery of the substance. The teaching of Hirano teaches an array of monomers to be used in the synthesis of homo- and co-polymers which include butyl acrylate, 2-ethylhexyl acrylate, acrylic acid and vinyl acetate. It would have been obvious to copolymerize these monomers as it stated by Hirano that the adhesive copolymer preferably contains monomers having the aforementioned chemical names. Additionally, the copolymer of 2-

ethylhexyl acrylate/ethylacrylate/vinyl acetate is taught in Example 2. As the ethyl acrylate of the copolymer is different from butyl acrylate by one carbon, one would expect similar properties between the two acrylic adhesives. The transdermal absorption promoters of the patches taught by Higo and Hirano include absorption enhancers such as lauryl alcohol, lactic acid and isopropyl. It is taught by Higo that these agents are useful because they promote transdermal delivery of active agents that possess a low diffusion constant for crossing the epidermal barrier. It would be obvious to one of skill in the art to include such absorption enhancers as they would necessarily increase the rate of bisoprolol across the skin, resulting in a higher plasma concentration resulting in improved pharmacological action. Moreover, as all of the references relied upon are within the same field of endeavor (i.e. transdermal delivery of active agents), it would have been obvious to one of ordinary skill in the art to combine them and arrive at a final product with the properties instantly claimed. Therefore, a matrix patch capable of delivering bisoprolol is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Conclusion

18. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

19. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/
Examiner, Art Unit 1611
February 19, 2009

/David J Blanchard/
Primary Examiner, Art Unit 1643